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MULTIPLE BIOCHEMICAL CORRELATES OF MANIC-DEPRESSIVE ILLNESS

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MULTIPLE BIOCHEMICAL CORRELATES OF MANIC-DEPRESSIVE ILLNESS*†

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IN AN EARLIER report [1] the results of a study of adrenal cortical activity changes in manic-depressive illness were presented. Two rapidly cycling manic-depressive patients had been studied in the hospital, untreated, through complete cycles by daily clinical assessment of their psychological state and by daily measurement of 24-hr urine 17-hydroxycorticosteroid (17-OHCS) excretion. It was found that mean decreases in adrenal cortical activity during mania relative to depression occurred, if at all, only in the latter part of hospitalization, after the patient had acclimated to the hospital. Plasma 17-OHCS were elevated during depression without concomitant increases in urine 17-OHCS. In addition, these patients had undergone metabolic turnover studies of radioactive tryptophan in an attempt to elucidate possible effects of differing levels of adrenal cortical activity on intermediary metabolism of tryptophan. An increase during depression in the radioactivity of urine kynurenine following infusion of ^{14}C tryptophan suggested an increased metabolism of tryptophan via the kynurenine pathway in depression, although 24-hr urine kynurenine was not concomitantly increased on the days of the tracer studies.

To provide further data on the somatic correlates of manic-depressive illness, the results of the following additional physiological and 24-hr urine biochemical measurements on these two patients are reported in this paper: daily 8 a.m. blood pressure and weight, and daily 24-hr urine volume, osmolality, creatinine, vanillylmandelic acid (VMA), kynurenine (KYN) and indoleacetic acid (IAA). Kynurenine and IAA, both urine tryptophan metabolites, were measured in an attempt to further clarify the intermediary metabolism of tryptophan in manic-depressive illness.

SUBJECTS AND METHODS

Clinical descriptions of the manic and depressive phases of both patients have been detailed in the earlier report [1], as have been the methods of urine collection and preservation. Blood pressure and weight were measured at 8 a.m., at the time the patients voided the last of the previous day's 24-hr specimen. A standard aneroid sphygmomanometer and clinical office scale were used for these measurements. Urine creatinine was determined by the standard method of Jaffe [2], urine VMA by the method of Pisano *et al.* [3], urine kynurenine by the ion-exchange method of Brown and Price [1, 4], and urine IAA by the chromatographic method of Armstrong *et al.* [5] followed by the colorimetric method of Fischl and Rabiah [6].

STATISTICAL ANALYSIS

The urine collections for the first patient were complete, since she was cooperative during all phases of her cycle; hence no correction factor for lost samples was applied to the values of the variables measured. However the second patient had a thought disorder component sufficient to

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obviate complete cooperation, and occasional individual specimens were lost on some days. These losses were confirmed by low urine volumes and creatinine values on these days without corresponding increases in osmolality. For Patient 2, therefore, all values of the variables measured were corrected to 2·0 g creatinine. The validity of creatinine correction of this patient's urine measurements has been discussed previously [1].

The phases of the manic-depressive cycles for each patient were determined from assessments by medical and nursing staff. The mean and standard deviation of each biochemical variable during each clinical phase was calculated, and two-tailed *t*-tests of significance between means were done for each variable for all clinical phases in each patient. Correlation coefficients and their significance levels were determined for each variable compared to each of the others throughout all days of hospitalization for each patient. Differences at the 0·05 level or less were considered significant.

RESULTS

Figure 1 shows the clinical periods and daily values for all parameters measured in Patient 1. The only discernible trend in blood pressure is a slightly narrower pulse pressure during depression. The patient's weight remained fairly stable throughout hospitalization. There is an apparent decrease in variability during depression of all urine measures.

Table 1 lists the clinical periods, number of days of each, and the means and standard deviations of each variable measured for Patient 1. (17-OHCS values, having been reported previously, are included for comparison.) Tables 2–7 are matrices of *t*-tests of these differences between means for each variable for each clinical period compared with the other periods.

With reference to the first three variables (Tables 1–4), mean urine volume was lowest during depression, significantly so compared to $mania_1$ and the two periods of euthymia. Mean urine creatinine was significantly lower during depression compared to all other clinical periods and was significantly higher during $euthymia_1$ compared to $mania_1$. Changes in mean urine osmolality were variable, and significant differences occurred only with $euthymia_2$ compared to $euthymia_1$ and depression.

With reference to the last three variables (Tables 1, 5–7), mean VMA excretion was significantly lower in depression compared to all other clinical periods and was significantly higher during $mania_2$ compared to $mania_1$. Mean kynurenine excretion was lowest during $euthymia_1$, significantly so compared to all other clinical periods, and was significantly lower during depression compared to both periods of mania. Mean IAA excretion during depression was higher than during mania, significantly so compared to $mania_1$. Mean IAA excretion was also significantly higher during $euthymia_2$ compared to $euthymia_1$, apparently on the basis of decreased variability of IAA excretion during these two euthymic periods rather than widely separated mean values.

Figure 2 shows the clinical periods and daily values for all parameters measured in Patient 2. There appears to be a gradual decrease in both systolic and diastolic blood pressure during depression. This patient's weight decreased at a steady rate during her hospital stay. The graphs of volume and osmolality indicate the values of the amounts of urine actually recovered. Since there were occasional urine samples lost, these data were not analyzed statistically. Creatinine excretion is graphed as a constant 2·0 g/24 hr, and the values for all other urine variables are graphed corrected to this constant. Table 8 lists the clinical periods, number of days of each, and the means and standard deviations of each variable measured for Patient 2. (Again 17-OHCS values, previously reported, are included for comparison.) Table 9 shows matrices of *t*-tests of these differences between means for each variable for each clinical period compared with the other periods.

Mean VMA excretion was significantly higher during mania compared to both euthymia and depression. Mean kynurenine excretion was significantly lower during depression compared to both mania and euthymia. Mean IAA excretion during depression was higher than during both mania and euthymia; significantly so compared to the latter clinical period.

Tables 10 and 11 are matrices of correlation coefficients and their significance levels for each biochemical variable for Patients 1 and 2 respectively. For Patient 1, as would be expected, volume correlated negatively with osmolality and positively with creatinine. Volume, and to a lesser extent creatinine, correlated positively to an increasing degree with 17-OHCS, kynurenine, and VMA in that order, but did not correlate with IAA. For both patients, there were no significant correlations between 17-OHCS and kynurenine or IAA, nor between IAA and kynurenine or VMA. For both patients VMA and kynurenine correlated positively to a significant degree. 17-OHCS and VMA did not correlate for Patient 1 but correlated positively to some degree for Patient 2. These correlation coefficients suggest that changes in urine volume may have partially influenced 17-OHCS and kynurenine excretion and may have influenced to a greater degree excretion of VMA. These data are consistent with the correlations between urine volume, osmolality, creatinine, 17-OHCS and VMA found for a third rapidly cycling manic-depressive patient during a 90-day hospitalization [7]. IAA excretion appears to have been independent from urine volume and creatinine excretion, a correlation

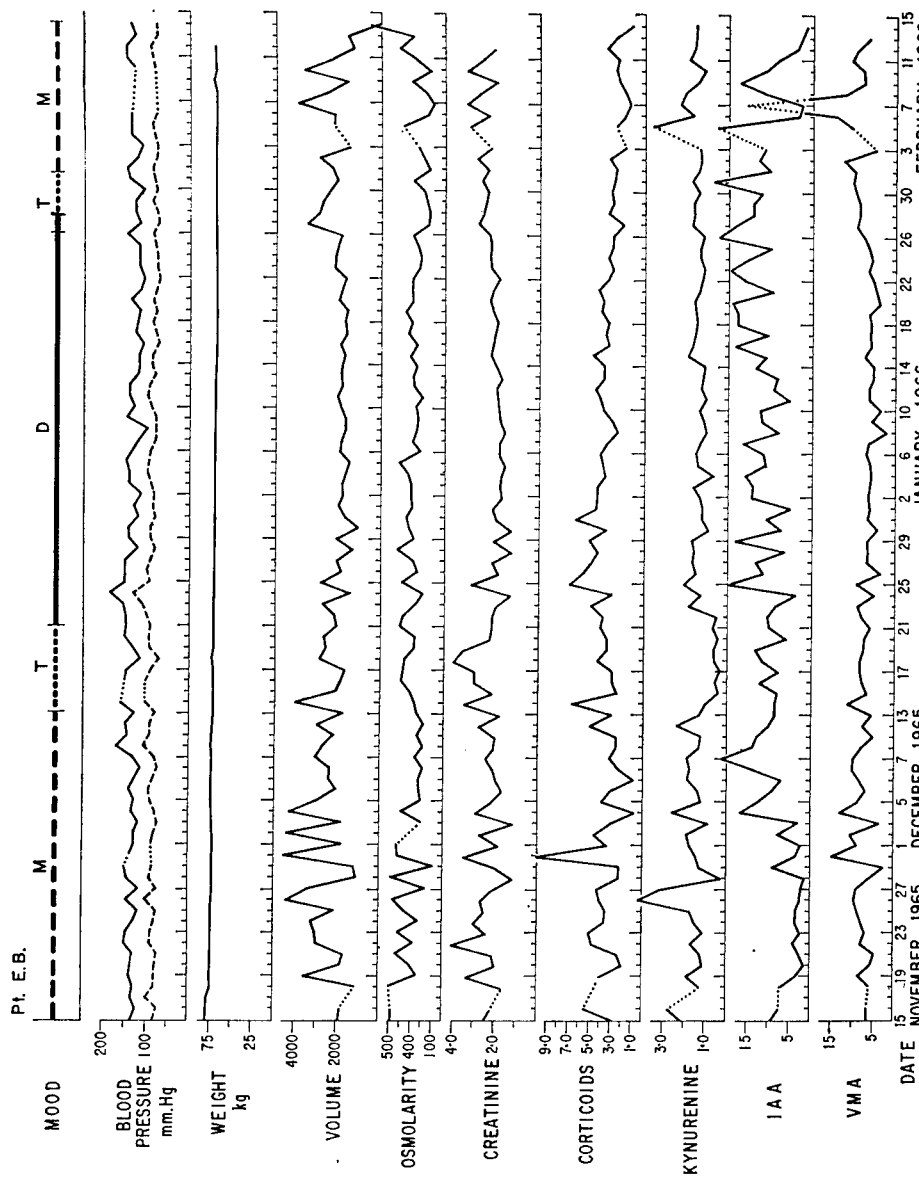

FIG. 1. Daily clinical ratings of mood, physiological, and 24-hr urine biochemical variables for Patient 1. M = mania, T = transition (euthymia), D = depression.

TABLE 1. MEANS AND STANDARD DEVIATIONS OF URINE BIOCHEMICAL VARIABLES MEASURED, PATIENT 1

Period	No. days	Volume (ml/24 hr)	Osmolality (mosm/l)	Creatinine (g/24 hr)	17-OHCS (mg/24 hr)	VMA (mg/24 hr)	Kynurenine (mg/24 hr)	IAA (mg/24 hr)
$Mania_1$	27	2620±973	303±116	2·33±0·63	3·53±1·78	7·63±2·56	1·75±0·79	6·73±5·21
$Euthymia_1$	8	2424±713	324±54	2·90+0·73	3·62±1·23	7·66±1·56	0·70±0·29	9·25±2·28
$Depression_1$	38	1931±459	300±62	2·00±0·35	4·00±0·97	5·70±1·44	1·35±0·33	12·28±4·54
$Euthymia_2$	3	2750±220	176±23	2·48±0·10	3·14±0·97	8·51±0·37	1·57±0·12	12·87±0·97
$Mania_2$	14	2186±904	283±146	2·68±0·50	2·43±0·66	11·27±7·29	1·79±0·60	9·77±6·95

TABLE 2. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE VOLUME FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
N.S.	< 0·001	N.S.	N.S.	Ma_1
	< 0·025	N.S.	N.S.	Eu_1
		< 0·01	N.S.	D_1
			N.S.	Eu_2

TABLE 3. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE OSMOLALITY FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
N.S.	N.S.	N.S,	N.S.	Ma_1
	N.S.	< 0·005	N.S.	Eu_1
		< 0·005	N.S.	D_1
			N.S.	Eu_2

TABLE 4. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE CREATININE FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
< 0·005	< 0·01	N.S.	N.S.	Ma_1
	< 0·001	N.S.	N.S.	Eu_1
		< 0·025	< 0·001	D_1
			N.S.	Eu_2

TABLE 5. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE VMA FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
N.S.	< 0·001	N.S.	< 0·05	Ma_1
	< 0·005	N.S.	N.S.	Eu_1
		< 0·002	< 0·001	D_1
			N.S.	Eu_2

TABLE 6. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE KYNURENINE FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
< 0·005	< 0·01	N.S.	N.S.	Ma_1
	< 0·001	< 0·005	< 0·001	Eu_1
		N.S.	< 0·005	D_1
			N.S.	Eu_2

TABLE 7. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE IAA FOR ALL CLINICAL PERIODS, PATIENT 1

Eu_1	D_1	Eu_2	Ma_2	
N.S.	< 0·001	N.S.	N.S.	Ma_1
	N.S.	< 0·05	N.S.	Eu_1
		N.S.	N.S.	D_1
			N.S.	Eu_2

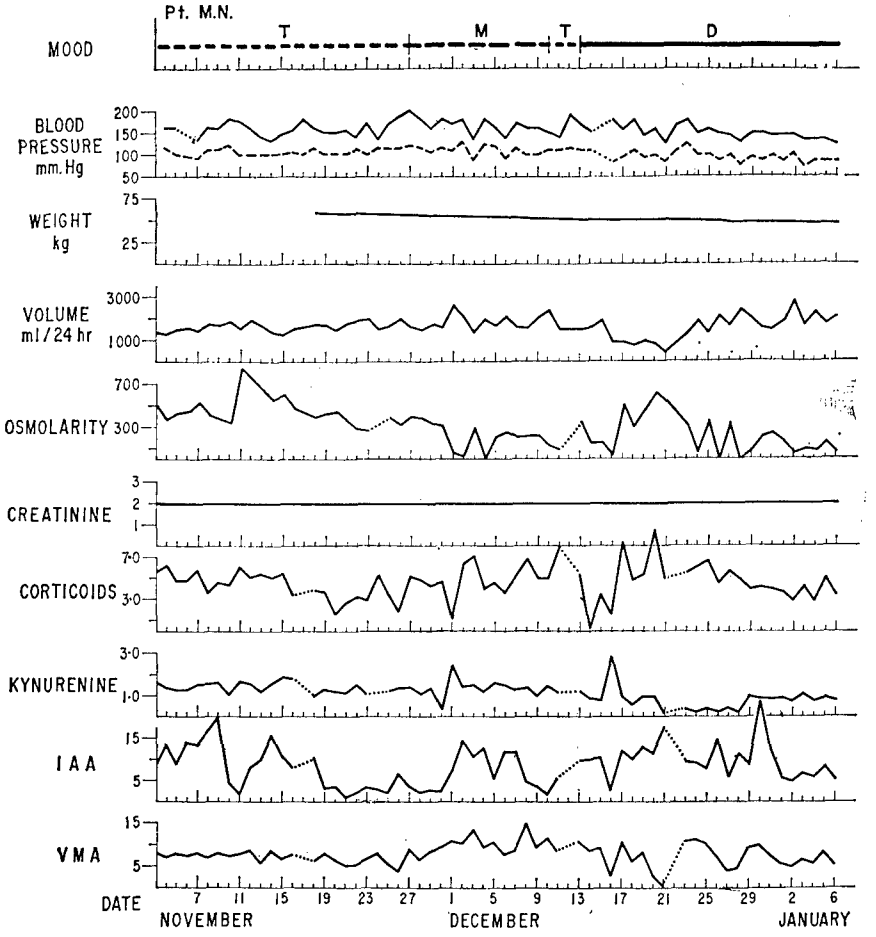

FIG. 2. Daily clinical ratings of mood, physiological, and 24-hr urine biochemical variables for Patient 2. M = mania, T = transition (euthymia), D = depression.

previously reported to be variably positive [8]. The positive correlation between VMA and kynurenine excretion in Patients 1 and 2 is probably on the basis of both these variables being partially volume dependent.

The partial volume dependency of kynurenine excretion suggests the possibility that the previously reported increases during depression in radioactivity of urine kynurenine following ^{14}C tryptophan infusion in both patients [1] may have been influenced by changes in urine volume. However, the volumes of the one-hour urines following the tracer infusions during depression in both patients were for the most part either the same as or less than the corresponding one-hour post-infusion volumes during mania and euthymia. Any volume dependency of kynurenine therefore would have tended to minimize the increases in kynurenine radioactivity found during depression.

TABLE 8. MEANS AND STANDARD DEVIATIONS OF URINE BIOCHEMICAL VARIABLES MEASURED (CORRECTED TO 2·0 g CREATININE), PATIENT 2

Period	No. days	17-OHCS (mg/24 hr)	VMA (mg/24 hr)	Kynurenine (mg/24 hr)	IAA (mg/24 hr)
$Euthymia_1$	25	4·64 ± 1·60	7·15 ± 1.16	1·39 ± 0·24	7·85 ± 5·18
$Mania_1$	11	4·84 ± 1·56	10·74 ± 2.09	1·41 ± 0·46	8·31 ± 4·19
$Depression_1$	24	4·75 ± 1·87	7·68 ± 2.88	0·79 ± 0·29	10·62 ± 4.55

TABLE 9. *t*-TESTS OF DIFFERENCES BETWEEN MEANS OF URINE BIOCHEMICAL VARIABLES FOR ALL CLINICAL PERIODS, PATIENT 2

Ma_1	D_1		Ma_1	D_1	
< 0·001	N.S.	Eu_1	N.S.	< 0·001	Eu_1
	< 0·005	Ma_1		< 0·001	Ma_1
	VMA			Kynurenine	
		Ma_1	D_1		
		N.S.	< 0·05	Eu_1	
			N.S.	Ma_1	
			IAA		

TABLE 10. CORRELATION COEFFICIENTS AND SIGNIFICANCE LEVELS OF URINE BIOCHEMICAL VARIABLES MEASURED DURING 90-DAY PERIOD, PATIENT 1

[Osm.]	Creat.	17-OHCS	VMA	KYN	IAA	
−0·44	+0·61	+0.24	+0·58	0·39	+0·02	Vol.
< 0·001	< 0·001	< 0·025	< 0·001	< 0·001	N.S.	
	0·00	+0·17	−0·19	−0·12	−0·08	[Osm.]
	N.S.	N.S.	N.S.	N.S.	N.S.	
		+0·12	+0·51	+0·21	+0·05	Creat.
		N.S.	< 0·001	< 0·05	N.S.	
			−0·07	+0·03	0·00	17-OHCS
			N.S.	N.S.	N.S.	
				+0·33	−0·10	VMA
				< 0·005	N.S.	
					+0·05	KYN
					N.S.	

TABLE 11. CORRELATION COEFFICIENTS AND SIGNIFICANCE LEVELS OF URINE BIOCHEMICAL VARIABLES MEASURED DURING 63-DAY PERIOD, PATIENT 2

VMA	KYN	IAA	
+0.27	−0·03	+0·22	17-OHCS
<0·05	N.S.	N.S.	
	+0·33	+0·06	VMA
	<0·01	N.S.	
		−0·04	KYN
		N.S.	

DISCUSSION

(i) *Blood pressure and body weight*

Patient 1 had a slightly decreased pulse pressure during her depressive phase, a time when she remained in bed constantly with considerably reduced physical activity. Patient 2 had a gradually decreasing systolic and diastolic pressure during the latter part of her depressive phase. This patient's physical activity was not diminished during depression, nor was her fluid intake reduced (urine volume was higher during the latter part of this period). Her gradually decreasing weight may be a possible but not likely explanation, since the weight loss had been occurring for the preceding five weeks (Fig. 2).

Both patients were maintained on the standard UCLA Medical Center house diet, but with a constant daily protein (100 g) and tryptophan content. Patient 1 maintained her weight during hospitalization; Patient 2, as mentioned, suffered a constant decrease in weight during her hospital stay. Whereas Patient 1 was cooperative enough to eat, drink and willingly participate in ward activities, Patient 2 had a thought disorder component during both manic and depressive phases sufficient to obviate her voluntarily maintaining her caloric intake. Apparently even coercive feeding by nursing staff was not enough to maintain her body weight. It is possible that this patient's gradual loss of lean body mass influenced the excretion levels of the biochemical variables measured [9, 10]. Because her weight loss was constant throughout hospitalization, any influence on the biochemical variables was most likely the same during all clinical periods, hence was probably not a significant factor influencing differences in urinary excretion levels between clinical periods.

(ii) *Volume, osmolality, creatinine*

Changes in urinary excretion of water and creatinine in manic-depressive illness have been discussed in the study of another rapidly cycling patient [7]. It was suggested that uncontrolled variations in water and sodium intake may explain inter-subject differences in the excretion of these variables. The low urine volume and creatinine excretions during depression in Patient 1 were most likely on the basis of reduced water intake during this period, a time when she remained constantly in bed. The variable changes in osmolality may have been a result of uncontrolled variations in sodium intake.

(iii) *VMA*

Changes in urine VMA excretion in manic-depressive illness have been discussed in the study of a third rapidly cycling patient [7]. It was suggested that the increases during mania in mean VMA excretion, as well as in the excretion of other catecholamine metabolites, were a reflection of heightened motor activity during mania compared to depression. Patient 1 had a significantly lower VMA excretion during depression compared to all other periods and a significantly higher VMA excretion during mania_2 compared to mania_1. Patient 2 had a significantly higher VMA excretion during mania compared to depression. In these two patients increased VMA excretion occurred during periods of increased physical activity.

The first patient's taking to bed during her depressive phase considerably reduced her physical activity. She was most active during her second period of mania, during which VMA excretion was high and quite variable (Table 1). She was in her first

manic period when she entered the hospital; nursing staff was quite interested in the early stages of research and handled her many demands with considerable deference. During $mania_2$, however, the ward nursing staff had reached their tolerance limits. Prompted by complaints from nursing administration and housekeeping staff about the deplorable condition of this patient's room (her 'pack-ratting' tendencies during mania have been described previously [1]), the ward staff cleaned her room several times a day. The patient responded with correspondingly increased efforts at hoarding and consequently increased physical activity. Her participation in the study was terminated before the end of $mania_2$ (Fig. 1) so that treatment of her illness might be begun. Patient 2, on the other hand, maintained about the same level of physical activity during depression as during euthymia, but was hyperactive to the point of combativeness during mania [1].

Whereas mean VMA and 17-OHCS excretion levels were inversely related in Patient 1 (Table 1), they were positively related in Patient 2 (Table 8). These findings suggest that there are inter-individual differences in patterns of physiologic activity in manic-depressive illness, at least as reflected in the urinary excretion of catecholamine and glucocorticoid metabolites. Intra-individual differences in patterns of physiologic activity as reflected by the excretion of these metabolites have been described previously for two juxtaposed periods of hypomania in the same rapidly cycling manic-depressive patient [7].

(iv) *Kynurenine*

The previously reported increase during depression in the radioactivity of urine kynurenine following infusion of ^{14}C tryptophan in both patients suggested an increased metabolism of tryptophan via the kynurenine pathway in depression, although 24-hr urine kynurenine was not concomitantly increased on the days of the tracer studies [1]. Indeed, as reported herein, both patients had significantly lower mean kynurenine excretion during depression compared to all periods of mania. This may have resulted from a heightened metabolism of kynurenine during depression since kynurenine is an intermediate metabolite in the degradation of tryptophan via this pathway. Cazzullo *et al.* [11] in a cross-sectional study, reported a significantly higher excretion of xanthurenic acid, another metabolite in this pathway, in 12 depressed patients compared to 6 manic patients. These data indicate the difficulty in making inferences about dynamic shifts (or blocks) [12] in metabolic pathways from the study of only a few intermediary metabolites. Ideally the enzymes involved in these pathways should be measured directly, as emphasized by Weber [13], but there are many methodologic difficulties readily apparent in such an approach. It appears that a reasonable compromise might be the measurement of as many intermediary and end metabolites as possible in the metabolic pathway(s) under study.

(v) *IAA*

Both patients had a higher mean IAA excretion during depression than during mania, but this difference was significant only for $depression_1$ compared to $mania_1$ in Patient 1. Previous studies of IAA excretion in psychiatric illness have involved primarily schizophrenic subpopulations. Both normal and increased IAA excretion in schizophrenics have been reported [14], and nonspecific influences such as dietary intake of tryptophan have been outlined [10]. Increased IAA excretion has been correlated with increased intensity of psychotic activity in schizophrenics [14]. This

finding is in contrast to the increased IAA excretion during depression in our patients, especially in Patient 1, whose level of psychotic activity decreased markedly when she took to bed during depression. Both the schizophrenic patients in Brune and Himwich's study [14, 15] and our manic-depressive patients were maintained on a constant 100 g protein per day diet, thereby minimizing dietary influence on changes in IAA excretion. In spite of a constant tryptophan intake, our patients evidenced considerable variability in daily excretion values during both manic and depressive periods. Such a large daily variability, if also present in schizophrenic patients, may help explain the conflicting results of previous studies.

Coppen *et al.* [16] found no significant change in mean 24-hr urine IAA excretion in a group of 13 depressed patients between depression and recovery. There was, however, considerable inter-subject variability in IAA excretion levels. Plasma tryptophan levels were the same during the phases of illness and recovery. Comparison of Coppen's data with ours is not possible except to say that there is both inter-subject and intra-subject variability in 24-hr IAA excretion in depression, even with constant dietary intake or plasma levels of tryptophan.

A possible explanation for the increased mean IAA excretion during depression in our patients is that there may be increased handling of tryptophan via the tryptophan (tyrosine) transaminase pathway which, like the pyrrolase pathway, is inducible by hydrocortisone. This mechanism was postulated previously [1] as an explanation for Coppen's finding of unchanged IAA excretion along with decreased tryptamine excretion in depression [16]. Radioactivity of urine IAA as well as of kynurenine after ^{14}C tryptophan infusion has been shown to be increased following ACTH injections in normal subjects [17]. However, the radioactivity of urine IAA was not increased during depression when this tracer technique was used in our manic-depressive patients, so that this explanation for increased IAA excretion during the depressive phases in these patients remains speculative.

The changes in the multiple biochemical variables reported in this study lend additional support to the concept of both inter-subject and intra-subject differences in patterns of physiologic activity in manic-depressive illness. The data highlight the difficulty inherent in inferring central mechanisms from the measurement of peripheral variables, even when longitudinal methodological designs are employed. In an attempt to elucidate underlying basic activity patterns in these patients multivariate analyses of both behavioral and biochemical measures have been done and will be the subject of another report [18].

SUMMARY

The purpose of this study was to investigate several biochemical parameters in manic-depressive illness in an attempt to elucidate changing patterns of physiologic activity with changes in mood. Two hospitalized rapidly cycling manic-depressive patients underwent daily clinical ratings of mood, daily measurements of blood pressure and weight, and daily 24-hr urine collections for creatinine, 17-hydroxy-corticosteroids (17-OHCS—reported previously), vanillylmandelic acid (VMA), kynurenine and indole-3-acetic acid (IAA). Mean daily excretion was calculated for each variable measured for each clinical phase. The following results were obtained and discussed:

1. Urine volume and creatinine excretion were lower during depression, most likely on the basis of reduced fluid intake.

2. VMA excretion was higher during mania and correlated with level of physical activity.

3. Kynurenine excretion was lower during depression, possibly on the basis of heightened metabolism of kynurenine during depression.

4. IAA excretion was increased during depression, although variations in daily levels during all phases were considerable.

The multiple biochemical variables herein reported suggest both inter-subject and intra-subject differences in patterns of physiologic activity in patients with rapidly cycling mood disorders. The results highlight the difficulty inherent in inferring central mechanisms from the measurement of peripheral variables.

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REFERENCES

1. RUBIN R. T. Adrenal cortical activity changes in manic-depressive illness: Influence on intermediary metabolism of tryptophan. *Arch Gen. Psychiat.* **17,** 671 (1967).
2. PETERS J. The determination of creatinine and creatine in blood and urine with photoelectric colorimeter. *J. Biol. Chem.* **146,** 179 (1942).
3. PISANO J. L., CROUT J. R. and ABRAHAM D. Determination of 3-methoxy-4-hydroxy-mandelic acid in urine. *Clin. Chim. Acta* **7,** 285 (1962).
4. BROWN R. R. and PRICE J. M. Quantitative studies on metabolites of tryptophan in the urine of the dog, cat, rat and man. *J. Biol. Chem.* **219,** 985 (1956).
5. ARMSTRONG M. D., SHAW K. N. F., GORTATOWSKI M. J. and SINGER H. The indole acids of human urine. Paper chromatography of indole acids. *J. Biol. Chem.* **232,** 17 (1958).
6. FISCHL J. and RABIAH S. Determination of free and total indole-3-acetic acid and of the indole index. *Clin. Chem.* **10,** 281 (1964).
7. RUBIN R. T., YOUNG W. M. and CLARK B. R. 17-Hydroxycorticosteroid and vanillylmandelic acid excretion in a rapidly cycling manic-depressive. *Psychosom. Med.* **30,** 162 (1968).
8. PSCHEIDT G. R., BERLET H. H., SPAIDE J. and HIMWICH H. E. Variations of urinary creatinine and its correlation to excretion of indole metabolites in mental patients. *Clin. Chim. Acta* **13,** 228 (1966).
9. FRIEDHOFF A. J. Biochemical effects of experimental diets. *J. Psychiat. Res.* **5,** 265 (1967).
10. MANDELL A. J. Some determinants of indole excretion in man. *Recent Adv. Biol. Psychiat.* **5,** 237 (1963).
11. CAZZULLO C. L., MANGONI A. and MASHERPA A. Tryptophan metabolism in affective psychoses. *Br. J. Psychiat.* **112,** 157 (1966).
12. PRICE J. M. Disorders of tryptophan metabolism. *Univ. Mich. Med. Bull.* **24,** 461 (1958).
13. WEBER G. *The Implications of Metabolic Adaptation for Behavioral Studies in Man,* read before the Annual Meeting of the American Association for the Advancement of Science, New York City, December (1967).
14. BRUNE G. G. Tryptophan metabolism in psychoses, *in* Himwich H. E., Kety S. S. and Smythies J. R. (Eds) *Amines and Schizophrenia,* Pergamon Press, Oxford (1967).
15. BRUNE G. G. and HIMWICH H. E. Biogenic amines and behavior in schizophrenic patients. *Recent Adv. Biol. Psychiat.* **5,** 144 (1963).
16. COPPEN A., SHAW D. M., MALLESON A., ECCLESTON E. and GURDY G. Tryptamine metabolism in depression. *Br. J. Psychiat.* **111,** 993 (1965).
17. MANDELL A. J. and RUBIN R. T. ACTH-induced changes in tryptophan turnover along induceable pathways in man, *Life Sci.* **5,** 1153 (1966).
18. RUBIN R. T. and OVERALL J. E. Multivariate analyses of manifest psychopathology and urine biochemical measures in manic-depressive illness. To be published.

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13. ABSTRACT

Several biochemical parameters were investigated in an attempt to elucidate changing patterns of physiologic activity with changes in mood in manic-depressive illness. Two hospitalized rapidly cycling manic-depressive patients underwent daily clinical ratings of mood, daily measurements of blood pressure and weight, and daily 24-hour urine collections for creatinine, 17-hydroxycorticosteroids (17-OHCS) vanillylmandelic acid (VMA), kynurenine, and indole-3-acetic acid (IAA). Mean daily excretion was calculated for each variable measured for each clinical phase. The following results were obtained and discussed: (1) Urine volume and creatinine excretion were lower during depression, most likely on the basis of reduced fluid intake. (2) VMA excretion was higher during mania and correlated with level of physical activity. (3) Kynurenine excretion was lower during depression, possibly on the basis of heightened metabolism of kynurenine during depression. (4) IAA excretion was increased during depression, although variations in daily levels during all phases were considerable. The multiple biochemical variables herein reported suggest both inter-subject and intra-subject differences in patterns of physiologic activity in patients with rapidly cycling mood disorders. The results highlight the difficulty inherent in inferring central mechanisms from the measurement of peripheral variables.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Psychiatry Mental illness Biochemical changes						